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| 09/780,532 | 02/09/2001 | Clive Wood | GNN-012CP | 8383 |

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7590 05/28/2009

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| EXAMINER |
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O HARA, EILEEN B

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| ART UNIT | PAPER NUMBER |
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1638

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05/28/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

09/780,532

Applicant(s)

WOOD ET AL.

Examiner

EILEEN B. O HARA

Art Unit

1638

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 March 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2,3,5,7,8,39-43,45-57 and 59-72 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2,3,5,7,8,39-43,45-57 and 59-72 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____.

DETAILED ACTION

Change of Examiner and Art Unit

1. The Examiner and Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1638 and Examiner Eileen O'Hara.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 11, 2009 has been entered.

Status of Claims

3. Claims 2, 3, 5, 7, 8, 39-43, 45-57 and 59-72 are pending in the instant application. Claims 69-72 were added in the amendment filed on March 11, 2009.

Withdrawn Rejections

4. Upon consideration of the claims, the specification and Applicants arguments submitted March 11, 2009, the previous rejections under written description and enablement are withdrawn, and new rejections are present below.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 43, 49, 53, 63, 70 and 72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5.1 Claim 43 is indefinite because it recites"

"The method of claim 42, wherein said TRADE polypeptide consists essentially of ***a polypeptide sequence at least 98% homologous to a polynucleotide*** encoding amino acids 1-168 of SEQ ID NO:2."

A polypeptide cannot be homologous to a polynucleotide, and therefore the claim is indefinite.

5.2 Claims 49, 53 and 63 are indefinite because the claims recite a "native TRADE α polypeptide in said cell comprising a sequence at least 95% homologous to SEQ ID NO: 2", "native TRADE α polypeptide in said cell having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 2", and "native TRADE α polypeptide in said cell comprising a sequence at least 95% homologous to SEQ ID NO: 2", respectively. It is not clear what is meant by the term "***native*** TRADE α polypeptide", or how one of ordinary skill in the art would be able to determine if a sequence is "a native polypeptide" or not by looking at it.

5.3 Claim 53 is also rejected because on line 5 of the claim, it recites "said polypeptide ***agent***", and there is no antecedent basis for this in the claim.

5.4 Claims 70 and 72 are indefinite because they recite ‘method of claim 2, wherein said TRADE polypeptide consists of SEQ ID NO: 2” and “method of claim 53, wherein said TRADE polypeptide consists of SEQ ID NO: 2”. It is not clear what TRADE polypeptide is being referred to. Claim 2 is a method of modulating activation of an NFkB signaling pathway in a cell comprising contacting a cell having “**TRADE activity**” with a soluble form of a TRADE polypeptide. Claim 2 does not specifically recite that the activity is of modulating the TRADE polypeptide of SEQ ID NO: 2. The polypeptide of SEQ ID NO: 2 is the full-length of the TRADE polypeptide, and would not be the soluble form, so it is not clear if the TRADE polypeptide consisting of SEQ ID NO: 2 is being modulated or is the modulator. Claim 72 is indefinite for the same reason.

5.5 Claims 53-57, 59-68, 71 and 72 are indefinite because claim 53 encompasses the extracellular domain is encoded by a polynucleotide that hybridizes under “**stringent**” conditions to the complement of nucleotides 1-504 of SEQ ID NO: 1. Though the specification on page 36 describes various hybridization and wash conditions, they are exemplary. The term **stringent** is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6.1 Claims 49, 53 and 63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a “*native* TRADE α polypeptide in said cell comprising a sequence at least 95% homologous to SEQ ID NO: 2”, “*native* TRADE α polypeptide in said cell having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 2”, and “*native* TRADE α polypeptide in said cell comprising a sequence at least 95% homologous to SEQ ID NO: 2”, respectively.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity and recitation that the polypeptide is a “native” polypeptide. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was

in possession *of the invention*. The invention is, for purposes of the ‘written description’ inquiry, *whatever is now claimed*.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF’s were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

There is only one human TRADE α polypeptide disclosed, that of SEQ ID NO: 2. No other native or naturally occurring TRADE α polypeptides are disclosed. Unless other naturally occurring variants of the polypeptide of SEQ ID NO: 2 are isolated, one of ordinary skill in the art would not know if a TRADE α polypeptide is native or not. Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 2, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

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6.2 Claims 2, 3, 5, 7, 8, 39-43, 457, 59-72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for *inhibiting* activation of the NFkB signaling pathway in a cell comprising contacting a cell *having a full-length TRADE protein of SEQ ID NO: 2 or SEQ ID NO: 4* with a soluble TRADE polypeptide, wherein the soluble form of the TRADE polypeptide comprises the extracellular domain of a TRADE α polypeptide, said extracellular domain comprising a polypeptide encoded by a polynucleotide at least 98% homologous to a poly nucleotide encoding amino acids 1-168 of SEQ ID NO: 2, wherein *inhibiting* of NFkB signaling *inhibits apoptosis* of said cell, does not reasonably provide enablement for a method for *modulating* activation of the NFkB signaling pathway in a cell comprising contacting a cell *having a TRADE activity* with a soluble TRADE polypeptide, wherein the soluble form of the TRADE polypeptide comprises the extracellular domain of a TRADE α polypeptide, said extracellular domain comprising a polypeptide encoded by a polynucleotide at least 98% homologous to a polynucleotide encoding amino acids 1-168 of SEQ ID NO: 2, wherein *modulation* of NFkB signaling modulates proliferation of said cell, or for said method wherein the extracellular domain is encoded by a polynucleotide that hybridizes under “**stringent**” conditions to the complement of nucleotides 1-504 of SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification teaches that the TRADE proteins when overexpressed ectopically activates the NFkB and JNK signaling pathways, which leads to apoptosis in cells. The TRADE proteins are orphan receptors, and the specification teaches that a TRADE-Fc fusion was made with the extracellular domain of TRADE, and that this “dimeric form is expected to be a potent,

soluble antagonist of the TRADE ligand” (page 131 of specification). Therefore the only “modulation” using the soluble extracellular domain of TRADE would be as a competitive inhibitor for the unknown ligand. Something that “modulates” can result in increased or decreased activity, but the only activity for the extracellular domain of TRADE would be to prevent activation by the ligand as taught in the specification, and hence decreasing NFkB signaling and decreasing cell death or apoptosis.

Additionally, claim 53 encompasses a TRADE extracellular domain that is encoded by a polynucleotide that hybridizes under stringent conditions to the complement of nucleotides 1-504 of SEQ ID NO: 1, and the specification teaches on page 36 that such a polynucleotide may have as little as 30% homology to the polynucleotide of SEQ ID NO: 1.

The instant specification discloses naturally occurring human TRADE proteins comprising the amino acid sequences presented in SEQ ID NO: 2 and 4, which have identical extracellular domains (amino acids 1-168). However, because the claims encompass the variants that can be encoded by a polynucleotide which can differ by as much as 70% to the polynucleotide encoding the TRADE extracellular domain of SEQ ID NO: 1, and only one polypeptide has been disclosed in the instant specification, a practitioner can not make a protein comprising an amino acid sequence other than the one disclosed in the instant specification and expect it to have the same functions. Some guidance is provided by the alignment between the human TRADE protein of the instant invention and the mouse TRADE protein (Fig. 4), which shows that there is 79% conservation of the amino acid residues between the two species. However, the instant specification does not identify those amino acid residues in the amino acid sequence of SEQ ID NO: 2 which are essential for its biological activity and structural integrity and those residues which are either expendable or substitutable. The problem of predicting

protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

In the absence of this information a practitioner would have to resort to a substantial amount of undue experimentation in the form of insertional, deletional and substitutional mutation analysis before they could even begin to rationally design a functional protein having other than a natural amino acid

sequence. The disclosure of a single DNA sequence encoding a single polypeptide with a natural amino acid sequence is clearly insufficient support under the first paragraph of 35 U.S.C. § 112 for claims which encompass the other variants. Even acknowledging high skill in the molecular biology art, prediction of which variants would have the same activity as TRADE is not possible based on the prior art or on the information provided in the specification, especially in light of the fact that the activity recited in the claims is “human OB-RGRP2 protein activity”, which is not clearly defined.

The current claim limitations are analogous to those of claim 7 of U.S. Patent Number 4,703,008 which were held to be invalid under 35 U.S.C. § 112, first paragraph, for want of enablement in *Amgen Inc. v. Chugai Pharmaceuticals Co. Ltd.*, 18 U.S.P.Q. 2d, 1016 (CAFC, 3/5/91, see page 1026, section D). In that instance, a claim to a nucleic acid encoding a polypeptide having an amino acid sequence sufficiently duplicative of the amino acid sequence of erythropoietin (EPO) so as to have a specified biological activity was held to be invalid under 35 U.S.C. § 112, first paragraph, for want of enablement. The disclosure upon which that claim was based described a recombinant DNA encoding EPO and a few analogs thereof. That disclosure differs from the instant specification because, whereas the instant specification describes a human TRADE protein, it does not describe even a single variant thereof. The court held that what is necessary to support claims of this breadth is a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of the claims. For proteins, that means disclosing how to make and use enough sequences to justify the grant of the claims sought. As indicated, the instant specification is even more limited than the '008 patent because it describes only a single protein and no analogs or mutants thereof and, therefore, provides even less support than the '008 specification for claims of comparable scope and which were held to be invalid in that patent.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

For the reasons discussed above, due to the large quantity of experimentation necessary to generate the large number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples and written description directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any specific functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

7. No claim is allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara whose telephone number is (571) 272-0878.

The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached on (571) 272-0975.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://portal.uspto.gov/external/portal/pair>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Eileen B. O'Hara/
Primary Examiner
Art Unit 1638